Clinical and Hormonal Effects of a Long-Acting Somatostatin Analogue in Pancreatic Endocrine Tumors and in Carcinoid Syndrome

JEAN-CHRISTOPHE SOUQUET, MD,*† GENEVIÈVE SASSOLAS, MD,‡ JACQUES FORICHON, PHD,* PASCAL CHAMPETIER, MD,* CHRISTIAN PARTENSKY, MD,* AND JEAN-ALAIN CHAYVIALLE, MD*

Nine patients with pancreatic apudomas (seven gastrinomas, one glucagonoma, one tumor secreting a substance P-like component) and nine with metastasized carcinoid tumors were treated with a somatostatin analogue (SMS 201-995), administered subcutaneously twice daily for 3 days. Treatment was pursued for 2 to 12 months in nine patients in whom SMS was clinically and/or biologically beneficial. In gastrinomas, SMS decreased plasma gastrin in all but one patient, inhibited the residual gastric acid secretion under H2-blockers and improved diarrhea; in the glucagonoma patient, glucagonemia decreased and skin lesions disappeared. In carcinoid syndrome, clinical efficacy was partial and inconstant; daily 5-hydroxyindole acetic acid (5-HIAA) output was slightly decreased. Plasma substance P levels decreased in six patients with initially high concentrations. No antitumoral activity or side effects have been so far evidenced. SMS 201-995 is a useful, well-tolerated agent in secreting pancreatic apudomas and to a lesser extent in carcinoid syndrome, where high-dosage regimens may be required.

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SOMATOSTATIN-14 inhibits the release of most regulatory gut peptides and exocrine pancreatic, gastric and intestinal secretions.[1,2] It also suppresses tumoral secretion by pancreatic and gut endocrine tumors.[3–5] However its clinical usefulness is hampered by its short half-life and the necessity of a continuous intravenous administration.[6] Moreover a life-threatening rebound effect sometimes occurs at the end of its administration.[7] Thus the natural tetradecapeptide can be used only for a short treatment period, for instance before or during surgery.[8] Synthetic analogues of somatostatin have been synthetized in order to increase the half-life and the clinical potency of somatostatin-14.[9] Long *et al.*[10] reported the short-term efficacy of Des AA^{1,2,4,5,12,13} D Trp^{8} somatostatin when administered by subcutaneous injection in eight patients with secreting pancreatic apudomas. SMS 201-995 is a recently developed long-acting somatostatin analogue that can be administered subcutaneously.[11] Several isolated reports have shown the clinical usefulness of this compound in digestive endocrine tumors,[12–15] in acromegaly due to pituitary adenoma,[16] and more recently in the malignant carcinoid syndrome.[17] We herein report on the biological and clinical efficacy of this compound when systematically tested in patients with digestive secreting endocrine tumors.

Patients, Materials and Methods

Patients

From November 1984 to December 1985, 18 patients gave informed consent for being included in the study. Their main clinical features and previous treatments are summarized in Table 1. Endocrine tumors were proved by histologic or cytologic studies of hepatic metastases and/or primary tumors in all but two patients. These two patients (Patients 4 and 5) had definite Zollinger-Ellison syndrome, but no detectable tumor at the time of evaluation: both had a typical clinical history with recurrent peptic ulcer, peptic esophagitis and diarrhea, increased basal acid secretion rates, and raised plasma gastrin levels (respectively, 98 and 60 pmol/l, N < 40 pmol/l), which significantly increased under secretin infusion (+245% and 253%, respectively). Celiac arteriography and abdominal computerized tomography (CT) scan evidenced no tumor.

From the *Service d'Hépatogastroentérologie and INSERM U 45, Hôpital Edouard Herriot, and ‡Centre de Médecine Nucléaire, Lyon, France.

† Supported by a grant from UFR Grange-Blanche.

Address for reprints: Jean-Christophe Souquet, MD, Service d'Hépatogastroentérologie, Pavillon Hbis, Hôpital Edouard Herriot, Place d'Arsonval, 69374 Lyon Cedex 08, France.

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TABLE 1. Clinical Features of the 18 Patients

Patient	Sex/age	Iry tumor	Metastases	Clinical features	Blood peptides	Previous treatments
1	M/42	Pancreas	Liver	Diarrhea	Gastrin, PP	Total gastrectomy, STZ + 5-FU
2	M/29	Pancreas	Liver, bones	Hypercorticism	Gastrin, ACTH	Total gastrectomy, left pancreatectomy
3	F/51	Pancreas	0	Ulcer, diarrhea	Gastrin	Ranitidine
4	F/71	Unknown	0	Ulcer, dysphagia	Gastrin	Cimetidine
5	M/46	Unknown	0	0	Gastrin	Total gastrectomy
6	F/38	Unknown	Liver	Ulcer, diarrhea	Gastrin	Left hepatectomy, ranitidine
7	F/68	Stomach	Liver	Diarrhea	Gastrin	Antrectomy, ranitidine
8	F/61	Unknown	Liver	Skin lesions	Glucagon	None
9	F/37	Pancreas	Liver, lung	Flushes	SP	Left pancreatectomy, STZ + 5-FU
10	M/39	Ileum	Liver, bones	Carcinoid Synd	Serotonin, SP	None
11	F/61	Ileum	Liver	Carcinoid Synd	Serotonin, SP	Surgery (ileum), STZ + 5-FU
12	M/56	Ileum	Liver	Carcinoid Synd	Serotonin, SP	Adriblastine + cisplatin
13	F/80	Ileum (?)	Liver	Carcinoid Synd	Serotonin	None
14	M/64	Unknown	Liver	Carcinoid Synd	Serotonin, SP	None
15	M/60	Ileum	Liver	Carcinoid Synd	Serotonin, SP	Right colectomy, hepatic artery ligature
16	M/82	Ileum	Liver	Carcinoid Synd	Serotonin, SP	None
17	M/74	Ileum (?)	Liver	Carcinoid Synd	Serotonin	None
18	M/55	Ileum	Liver	Carcinoid Synd	Serotonin	STZ + 5-FU, right colectomy

M: male; F: female; Carcinoid Synd: carcinoid syndrome; PP: pancreatic polypeptide; ACTH: adrenocorticotropin; SP: substance P-like immunoreactivity; STZ + 5-FU: streptozotocin (500 mg/m^2 J) and 5-fluorouracil (400 mg/m^2/J) during 5 dys every 6 weeks.

Patient 3 had a multiple endocrine neoplasia syndrome type 1 with pancreatic gastrinoma, pituitary adenoma and parathyroid hyperplasia.

Patient 4 refused explorative laparotomy. Patient 5 had had three previous gastric operations leading to total gastrectomy without the primary tumor being discovered.

Carcinoid syndrome was severe in all nine patients with diarrhea (more than four stools/day), flushes, chronic facial erythema, and tricuspid regurgitation proved by echocardiography. Blood serotonin and 24-hour urinary 5-hydroxyindole acetic acid excretion (5-HIAA) were significantly elevated. Six patients also had elevated plasma levels of substance P-like immunoreactivity.

Procedure of Treatment With SMS 201-995

Systematic hormonal evaluation including measurement of plasma somatostatin, gastrin, vasoactive intestinal peptide (VIP), substance P, pancreatic polypeptide, thyrocalcitonin, parathormone, adrenocorticotropin, glucagon, insulin and serotonin levels, and of urinary 5-HIAA output was realized in all patients before treatment to draw the pattern of tumoral hormone and amine secretion. Those and the patients' symptoms were monitored over a 3-day control period. In patients with carcinoid syndrome only 5-HIAA was determined on a day to day schedule. SMS 201-995 (Sandoz, Basel, Switzerland) was then administered for 3 days as a twice daily subcutaneous 100-μg injection. The same clinical and hormonal criteria were again followed daily during this acute phase of the treatment. Blood hemoglobin, urea, creatinine, electrolytes, glucose, liver function tests and leukocyte count were assessed on the first day of control period and on the last day of SMS administration. Due to their serious conditions, all patients were maintained under their previous medical treatment, which was H2-blockers (cimetidine or ranitidine) for patients with gastrinomas and loperamide and/or methysergide for those with carcinoid syndrome.

If clinically beneficial, SMS 201-995 was pursued at the same dose with monthly clinical and hormonal reevaluation. This phase will be referred to as chronic phase of the treatment.

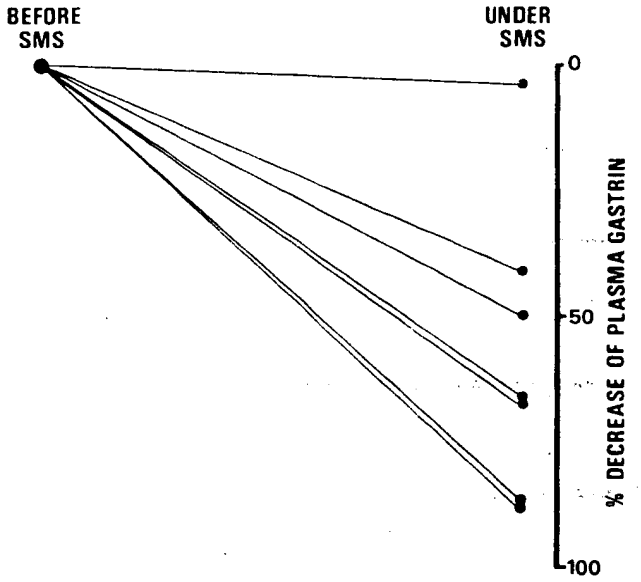

FIG. 1. Effect of a 3-day treatment with SMS 201-995 (100 μg subcutaneously twice a day) on plasma gastrin levels in seven patients with Zollinger-Ellison syndrome. This effect is expressed as (mean of three values during treatment ×100)/(mean of three values before treatment). Plasma gastrin was assayed in samples drawn at 8:00 AM, namely 12 hours after the last analogue injection.

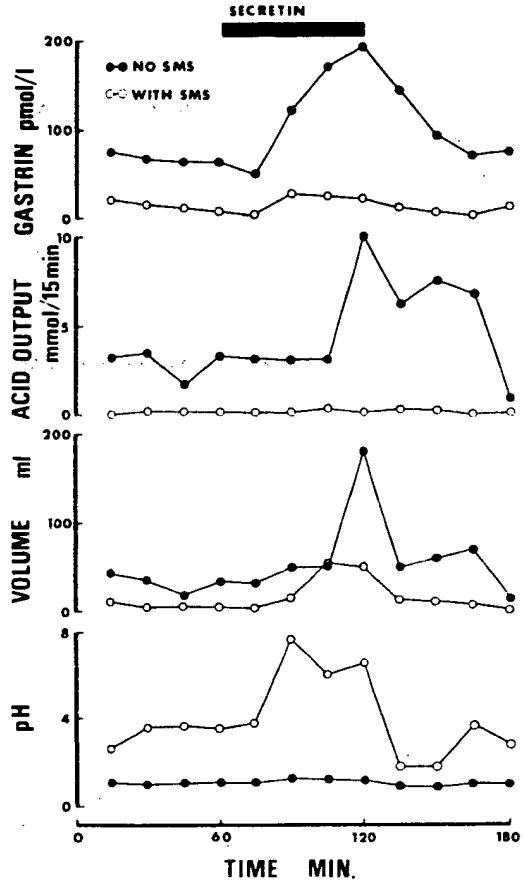

FIG. 2. Effect of SMS 201-995 on plasma gastrin levels, pH, volume, and acid output of gastric secretion during a secretin test in a patient with Zollinger-Ellison syndrome. Secretin was perfused during 1 hour at 3 $\mu g\ kg^{-1}\ hr^{-1}$. Volume and pH of acid secretion were determined every 15 minutes. SMS 201-995 (100 μg sc) was administered 1 hour before the test.

Methods

Blood samples for gut peptide assays were drawn at 8:00 AM from fasting subjects in chilled tubes containing heparin and aprotinin (400 Kallikrein inactivator units [KIU]/ml). Blood was quickly centrifugated and plasma was kept at −30°C until assays. Gut hormones were measured by previously reported radioimmunoassays.[18-20] Results for peptide assays are expressed as pmol synthetic peptide/l. Urine for 5-HIAA determination was collected over 24 hours. Acid secretion was determined with standard methods for a 1-hour period starting at 11:00 AM 3 hours after SMS 201-995 administration. H2-blockers also were given at 8:00 AM. Secretin provocation test consisted of 1-hour infusion of GIH secretin (Kabivitron) (3 $\mu g\ kg^{-1}\ hr^{-1}$).

Results

Patients With Gastrinoma

Acute treatment: The median plasma gastrin level in the fasting state was 187 pmol/l (range, 47–2990 pmol/l). In all but one patient, SMS 201-995 resulted in decreased gastrin levels with a mean variation of 58% below pretreatment values (range, 4%–88%, n = 7; $P = 0.003$, Fig. 1). Only the patient with the higher concentrations (above 2900 pmol/l) showed no significant improvement (4%). Four patients had normal gastrin levels after 3 days (<40 pmol/l). The effect of SMS 201-995 was already clear on the first day of treatment.

In Patient 4, a secretin test was performed before and during SMS 201-995 administration: gastrin levels fell within the normal range and remained so during secretin infusion. The effect of SMS during this test is illustrated in Figure 2.

In the four patients with no previous gastric surgery, acid secretion was studied before SMS treatment and 3 hours after the morning SMS 201-995 administration on the third treatment day: gastric acid secretion was almost completely inhibited in all of them with a rise of intragastric pH above 6 (Table 2) whereas the inhibitory effect of H2-blockers alone (cimetidine or ranitidine) on acid secretion was only partial. Volume of gastric secretion also was reduced in three patients (Table 2).

The acute efficacy of SMS 201-995 on clinical symptoms in gastrinoma patients was inconstant: no clear effect was found on diarrhea in the four patients with this symptom, but epigastric pain was improved in two of three patients.

TABLE 2. Effect of SMS 201-995 on Gastric Acid Secretion in Four Patients With Zollinger Ellison Syndrome

		No SMS			With SMS		
Patient	Treatment	Acid output (mmol/h)	pH range	Volume (ml)	Acid output (mmol/h)	pH range	Volume (ml)
3	Ranitidine 150 mg	1.5	1.5–1.8	48	0.5	3.5–5.2	18
4	Cimetidine 400 mg	5.4	1.3–1.4	113	0.05	5.0–6.9	48
6	Ranitidine 300 mg	12.0	1.2–1.3	121	0	7.0–7.7	51
7	Ranitidine 150 mg	2.6	3.9–5.6	66	0	7.2–8.1	78

Ranitidine or cimetidine was given orally at 8:00 AM; SMS 201-995, 100 μg, was administered simultaneously. Acid secretion was measured between 11:00 and 12:00 AM.

Patient 1 had elevated plasma pancreatic polypeptide levels (330 pmol/l; N < 250 pmol/l), which showed no decrease along the 3-day period. In Patient 2, a Cushing's syndrome was due to adrenocorticotropic hormone (ACTH)-like peptide secretion by hepatic metastases. The 3-day treatment did not improve diabetes, but 24-hour free urinary cortisol slightly decreased from 8395 to 7051 pmol (mean of three determinations). Plasma ACTH level showed no clear modification on single pre- and under-SMS treatment estimates.

Chronic treatment: As adjunction of SMS 201-995 to H2-antagonists improved control of acid secretion, the four patients with intact stomachs (Patients 3, 4, 6, and 7) were given a chronic treatment. The reasons for this approach were as follows: Patient 3 had a multiple endocrine neoplasia (MEN) type 1 and a melanoma; Patient 4 refused surgery; Patient 6 showed multiple recurring liver metastases after left hepatectomy; and Patient 7 had several hepatic secondaries, and had previously had nephrectomy which made chemotherapy by cisplatin or streptozotocin hazardous. In the four patients, SMS 201-995 has been administered along regular doses of H2-antagonists and has been given so far for 1 month in Patient 6, 2 months in Patient 4, 5 months in Patient 7, and 12 months in Patient 3. It has prevented ulcer recurrence, epigastric pain, recurrent dysphagia by esophageal peptic stenosis (Patient 4) and totally stopped diarrhea. Plasma gastrin has remained within the normal range during the treatment in three patients (Patients 3, 4, and 7) and slightly elevated in Patient 6.

Other Pancreatic Endocrine Tumors

A 30-year-old woman had an endocrine pancreatic tumor with elevated plasma substance P-like immunoreactivity; she experienced some flushes (about one a day). Plasma substance P level was moderately decreased by SMS 201-995 during the 3-day test period (436–277 pmol/l; N < 40 pmol/l). No chronic treatment was undertaken.

The last patient had a glucagonoma with hepatic metastases, typical severe skin lesions and high plasma glucagon levels (1000–1300 pmol/l). SMS 201-995 decreased plasma glucagon to 430 pmol/l. Skin lesions disappeared within 3 weeks although plasma glucagon was not normalized. She then was treated simultaneously by chemotherapy with streptozotocin (500 mg/m2/j) and fluorouracil (400 mg/m2/j) for 5 days every 6 weeks. After the second chemotherapy session, glucagon was under 300 pmol/l and the patient dropped out of the SMS 201-995 treatment. Fifteen days later, necrolytic erythema reccurred and again was controlled within two weeks by readministration of SMS 201-995 at the same dose (100 μg twice daily). After five chemotherapy sessions and 8 months of SMS 201-995 treatment, she has not experienced new skin lesions in spite of persisting hepatic metastases and of moderate hyperglucagonemia (115 pmol/l).

Patients with Carcinoid Syndrome:

Acute treatment: Urine 5-HIAA output was elevated in the nine patients before treatment (median, 761 μmol/24 hours; range, 168–2197 μmol/24 hours [normal < 40 μmol/24 hours]). SMS 201-995 slightly decreased 5-HIAA excretion (mean variation = 31% ± 7%, n = 9; $P = 0.057$). In no case did normalization of 5-HIAA occur. Plasma substance P-like immunoreactivity was increased in six of the nine patients (median, 262 pmol/l; range, 88–1091 pmol/l; N < 40 pmol/l) and was clearly reduced by SMS 201-995 in all patients, with complete normalization in three of them.

Diarrhea was clearly improved but did not disappear in four patients (Patients 10, 14, 16, 18) with decrease in bowel movements (about two stools a day) and increase in stool consistency. Two patients showed a slighter improvement (Patients 11 and 15). The last three patients did not report any benefit. Effects on flushes were less marked: partial improvement was recorded by three patients (Patients 10, 14, and 18) and a slight effect was noticed in one (Patient 16). No effect was noted on chronic erythema.

Chronic treatment: This was given to the six patients who displayed at least a slight beneficial effect. Due to the lack of dramatic improvement, we decided to perform other treatment procedures (chemotherapy, hepatic arterial chemoembolization) simultaneously so that interpretation of SMS 201-995 long-term efficacy is not straightforward. Among the six patients, two (Patients 11 and 15) showed no clear benefit and therefore stopped treatment after 2 months. For the four others, the partial clinical improvement (stool frequency and consistency) persisted for period of 3 to 13 months, even if simultaneous treatments apparently were only slightly effective. As an example, Figure 3 shows the course of the two patients with the longest follow-up. Patient 10 was treated with adriblastine and cisplatin every 4 weeks. Although there was no decrease in the size of liver metastases, and although 5-HIAA output slowly increase with time, 5-HIAA clearly remain under pretreatment values. In Patient 12, SMS treatment was pursued until surgery (liver metastasectomy). Then SMS was interrupted and regular courses of chemotherapy were administered for 8 months.

The patient again was treated successfully with the somatostatin analogue but the dose had to be increased to 300 μg twice a day to maintain clinical benefit. Symptoms (flushes and diarrhea) increased when SMS was decreased inadvertently to 200 μg twice a day. In contrast Patient 14 increased the dose to 200 μg twice a day without improvement as compared to 100 μg twice a day.

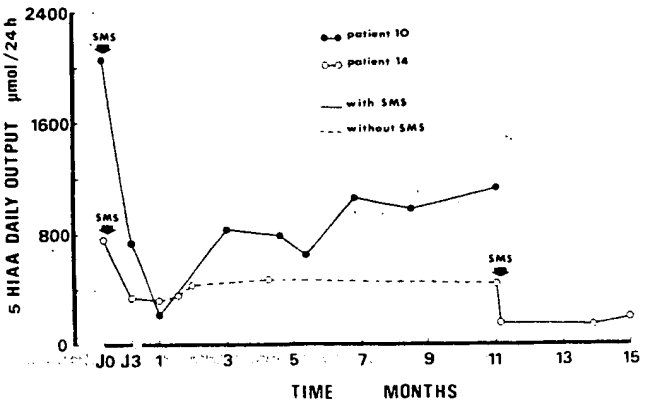

FIG. 3. Long-term evolution of 24-hour urine 5-HIAA output under chronic administration of SMS 201-995 in two patients with metastasized carcinoid tumors. Patient 10 was treated by chemotherapy (cisplatin and doxorubicin); Patient 14 had hepatic metastasectomy followed by chemotherapy (5-fluorouracil). During this period (- - -), SMS was not given and was again administered at month 11. J0 mean value of 5-HIAA output during the 3-day control period; J3: mean value of 5-HIAA output during the first 3 days of SMS treatment.

Antitumoral Effect

Three patients have now been treated for more than 8 months. Two patients with a gastrinoma and a carcinoid tumor, respectively, have no antitumoral effect of SMS 201-995 as judged from recent CT scan evaluation. In the glucagonoma patient, there was a marked reduction in the size of liver metastases, but the patient had simultaneously received chemotherapy.

Adverse Effects

No adverse effects, except occasional pain at the injection site, have been noticed by patients. No effect on standard blood tests has been recorded, especially on glucosemia. No clinical rebound effect occured upon cessation of treatment.

Discussion

The inappropriate secretion of peptides or amines by endocrine tumors may induce life-threatening clinical manifestations.[21,22] On the other hand tumor growth usually is slower than for nonendocrine neoplasms. Since curative surgery often is impossible and sensitivity to chemotherapy unpredictable, suppression of hormonal release and/or of the effects of inappropriately secreted peptides or amines is an important goal in the management of these tumors.[21,22]

Several groups have already shown that SMS 201-995 or minisomatostatin[23] could reduce peptide related symptoms for at least a short time period in isolated cases of gastrinoma,[24] vipoma,[14,15,25] insulinoma,[13] growth hormone-releasing factor secreting pancreatic tumor,[12] and in growth hormone secreting pituitary adenoma.[16] Only one report deals with eight digestive endocrine tumors, a single patient being treated for more than 3 days.[26] The clinical and biochemical efficacy of SMS 201-995 was here systematically studied in 18 patients during 3 days, and for periods longer than 2 months in nine patients. This study demonstrates that the minisomatostatin, given subcutaneously, produces effective suppression of inappropriate secretions by most digestive endocrine tumors and to a lesser extent by metastases of carcinoid tumors.

As in healthy volunteers,[27] SMS 201-995 powerfully inhibited gastric acid secretion in patients with Zollinger-Ellison syndrome. Its effect is mediated by an inhibition of gastrin release and probably by a direct action on parietal cells since gastric secretion was completely inhibited although plasma gastrin levels did not always return to normal values. Gastrin levels were almost constantly decreased: in the only patient with no effect, a small inhibition could be missed in such a short protocol due to variability of very high gastrin concentrations from day to day. Gastrin release inhibition in this study was significant 12 hours after the last subcutaneous injection at a time where biological activity of minisomatostatin is greatly reduced due to its short half-life.[11] Thus it appears that two injections a day is sufficient for significant reduction of hormonal release in patients with gastrinoma.

As reported by others after the prolonged use of SMS 201-995 in two cases of gastrinoma,[24,28] the inhibitory effect of the minisomatostatin showed no trend to decrease along time in the current patients treated for periods of 2 to 11 months.

Thus SMS could be a new therapeutic modality in the treatment of gastrinoma. Gastrectomy, which was the only treatment of metastasized gastrinoma until recently, could be avoided with H2-blockers or omeprazole, the new H+ pump blocker. However the former often became inefficient with time and have important side effects at high dose, whereas the later has not yet been thoroughly evaluated as to long-term efficacy and side effects. As the minisomatostatin appeared well-tolerated (no rebound effect and specifically no hyperglycemia in spite of the fact that SMS 201-995 inhibits insulin release in healthy volunteers[29] and in insulinoma patients,[13] SMS 201-995 could be associated with regular doses of H2-blockers and dramatically improve the control of gastric acid secretion.

Former therapy of skin lesions of glucagonoma necessarily required surgery or chemotherapy; subsequently somatostatin-14 was shown to improve skin lesions in glucagonoma patients.[30] Wood *et al.*[26] reported a decrease of blood glucagon but no effect on necrolytic erythema

within 3 days of SMS 201-995 therapy. This discrepancy with the dramatic improvement of skin lesions achieved in the current case could be explained by the fact that a 3-week treatment by minisomatostatin was necessary to obtain this improvement. The beneficial role of minisomatostatin was further attested by the rapid recurrence of skin lesions when the patient decided to drop out.

Natural somatostatin-14 has been shown to prevent flushes and to decrease diarrhea in carcinoid tumors.[4] Accordingly SMS has been reported to help control carcinoid crisis during surgery.[31] In the current nine patients with severe carcinoid syndromes, SMS gave only an inconstant and partial clinical and biological benefit. The effect was more marked on stool frequency and consistency than on flushes and chronic erythema. The decrease of 5-HIAA excretion was usually limited but was present in most of the patients, whereas in the only carcinoid patient of Wood *et al.*[26] there was no decrease of 5-HIAA output. Kvols *et al.*[17] recently described the effect of the minisomatostatin in 25 patients with carcinoid syndrome. They obtained a greater improvement in stool frequency and in flushing, but used higher doses than we did, *e.g.*, 450 μg/d *versus* 200 μg/d. However they could not reach complete clinical and biochemical response. Moreover if our Patient 12 was improved by doses of 600 μg/d, Patient 14 was not better after an increase of SMS posology to 400 μg/d. Possibly very high SMS 201-995 daily doses would give a better controlled diarrhea, but also more side effects such as the steatorrhea recorded in some patients of Kvols *et al.*[17] Finally SMS appeared to give only a temporary clinical relief as the disease progresses. Thus the minisomatostatin has to be used along other treatment procedures of carcinoid metastases.

The inhibition of peptide and amine release achieved with the analog suggests that tumoral cells retain some functional somatostatin receptors, which however remain to be characterized. The number and types of these receptors could vary among tumors (especially in pancreatic apudomas *versus* carcinoid liver metastases) and account for the variable efficacy of SMS 201-995. The drug acted differently on gastrin and pancreatic polypeptide secretion in one patient and reduced the secretion of substance P-like immunoreactivity more than the secretion of serotonin in other patients with carcinoid syndrome. These data suggests the existence of several pathways inside tumoral cells for control of different secretions, or the presence of different subpopulations of cells with variable sensitivity to SMS 201-995.

Experimental[32,33] and clinical[17,27,34] data suggest that somatostatin and SMS 201-995 could have an antitumoral effect in digestive tumors. No such effect was recorded here in the preliminary series of three patients for more than 10 months.

In conclusion the current study shows that a long-acting somatostatin analogue (SMS 201-995), is an easy-to-use and well-tolerated new therapeutic agent. It is most useful for the control of symptoms in secreting pancreatic endocrine tumors such as gastrinomas and glucagonomas. Although its effects in carcinoid syndrome are far from dramatic, the component may be tested systematically at this and higher doses along other treatments in order to select patients in whom long-term benefit may be expected on symptom severity. Longer and larger trials have to be realized to evaluate the antitumoral effect of SMS 201-995.

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